HIGH PRODUCTION VOLUME (HPV)

CHEMICALS CHALLENGE PROGRAM

TEST PLAN

For

4-NITROPHENOL

CAS NO. 100-02-7

Prepared by:

Solutia, Inc. Registration No.

575 Maryville Centre Drive,
St. Louis, Missouri 63141

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EXECUTIVE SUMMARY

Solutia Inc. voluntarily submits the following screening information data and Test Plan covering the chemical, 4-Nitrophenol, also known as para-Nitrophenol or PNP (CAS No. 100-02-7), for review under the Environmental Protection Agency's High Production Volume (HPV) Chemicals Challenge Program.

A substantial amount of data exists to evaluate the potential hazards associated with PNP. Use of key studies or estimation models available from data already developed provide adequate support to characterize each Endpoint in the HPV Chemicals Challenge Program without the need for additional, unnecessary testing.

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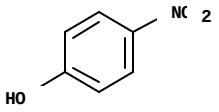
TEST PLAN FOR P-NITROPHENOL (PNP)

I. INTRODUCTION AND IDENTIFICATION OF CHEMICAL

Under EPA's High Production Volume (HPV) Chemicals Challenge Program, Solutia Inc. has committed to voluntarily compile basic screening data on Phenol, 4-nitro-, or PNP. The data included in this Test Plan provide physicochemical properties, environmental fate, and human and environmental effects of PNP, as defined by the Organization for Economic Cooperation and Development (OECD). The information provided comes from existing data developed on behalf of Solutia Inc. or found in the published scientific literature and fulfills Solutia's obligation to the HPV Challenge Program.

A. Structure and Nomenclature

Following is a structural characterization of PNP and associated nomenclature.



Phenol, 4-nitro-

CAS No. 100-02-7
Synonyms: 4-Hydroxynitrobenzene; p-Nitrophenol; para-nitrophenol; PNP

B. Manufacturing & Use

PNP is manufactured by a single US producer, Solutia Inc., at a single manufacturing site. The manufacturing operation is a closed, continuous process. Only a few employees are involved in its manufacture and have minimal potential for skin or airborne exposure, which occur chiefly during material transfer operations. Due to the high acute hazards associated with its potential to cause methemoglobinemia, specific manufacturing procedures and practices have been established to minimize the exposure potential to PNP.

p-Nitrophenol is sold to a limited number of customers at a few US processing sites and exported to ex-US sites for the express purpose of full chemical conversion into other

industrial chemicals. As such, PNP is expected to chemically react to form chemicals used as dyes/pigments, pharmaceuticals, analgesics and adhesives. There are no known or suspected consumer exposures to PNP resulting from TSCA-related activities, as PNP is consumed as a chemical intermediate. Loss to the atmosphere or from non-POTW aqueous streams during manufacturing or processing is minimal. Hence, very limited occupational or environmental exposure is expected to occur.

II. TEST PLAN RATIONALE

The information obtained and included to support this Test Plan have come from either 1) internal studies conducted by/or for Solutia Inc. (or its predecessor Monsanto Co.), 2) have been extracted from the scientific literature either as primary references or as found in well-accepted, peer-reviewed reference books, or 3) were estimated using environmental models accepted by the US EPA (1999b) for such purposes. This initial assessment includes information on physicochemical properties, environmental fate, and human and environmental effects associated with PNP. The data used to support this program include those Endpoints identified by the US EPA (1998a); key studies have been identified for each data Endpoint and summarized in Robust Summary form and included in Section VI. of this Dossier.

All studies were reviewed and assessed for reliability according to standards specified by Klimisch *et al* (1997), as recommended by the US EPA (1999a). The following criteria were used for codification:

1. Reliable without Restriction - Includes studies which comply with US EPA and/or OECD-accepted testing guidelines, which were conducted using Good Laboratory Practices (GLPs) and for which test parameters are complete and well documented,

2. Reliable with Restrictions – Includes studies which were conducted according to national/international testing guidance and are well documented. May include studies conducted prior to establishment of testing standards or GLPs but meet the test parameters and data documentation of subsequent guidance; also includes studies with test parameters which are well documented and scientifically valid but vary slightly from current testing guidance. Also included were physical-chemical property data obtained from reference handbooks as well as environmental endpoint values obtained from an accepted method of estimation (i.e. EPIWIN).

3.Not Reliable – Includes studies in which there are interferences in either the study design or results that provide scientific uncertainty or where documentation is insufficient.

4. Not Assignable – This designation not used in this Dossier.

Those studies receiving a Klimisch rating of 1 or 2 are considered adequate to support data assessment needs in this Dossier. Additional studies have been identified during our literature search on the referenced HPV endpoints but have not been summarized in this Dossier. The reader is referred to three additional data compendia which also summarize available data on the physical-chemical properties, ecotoxicity, environmental fate and health effects of p-nitrophenol. These include the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000), the ECB IUCLID Dossier for p-Nitrophenol (2002), and the Hazardous Substances Data Bank (HSDB) (2002) for p-Nitrophenol.

II. TEST PLAN SUMMARY AND CONCLUSIONS

Conclusion: All HPV Endpoints have been satisfied with data from studies that were either well documented, used OECD guideline methods and conducted in accord with GLPs, or were estimated from acceptable estimation modeling programs. Hence, no further testing for any of the HPV Endpoints is deemed necessary (Table 1).

Physical-chemical property values (Melting Point, Boiling Point, Vapor Pressure, Partition Coefficient and Water Solubility) were obtained from reputable references and cited as an Accepted or Peer Reviewed value in the PNP Hazardous Substances Data Bank (2002) and/or IPCS CICAD on Mononitrophenols (2000). These endpoints have been classified as "2-Reliable with restrictions".

Environmental Fate values for Transport (Fugacity) were obtained using a computer estimation –modeling program (EPIWIN, 2002) recommended by EPA; they have been classified as "2-Reliable with restrictions". Biodegradation data were summarized in a published article reporting results of multiple studies following OECD # 301/GLP guidance and thus classified as "1-Reliable without restriction". Photodegradation data was obtained from a published study following EPA test guidelines and was considered "2-Reliable with restrictions". In keeping with OECD SIDS guidance, no testing for Stability in Water is planned with PNP as it is generally recognized as "stable" in aqueous solutions.

Ecotoxicity Endpoints were met with studies that were conducted according to OECD guidelines for Acute Invertebrate Toxicity (OECD 202) and Acute Plant Toxicity (OECD 201), or conducted according to study design and test parameters which preceded, but were consistent with OECD test guidance (Acute Fish Toxicity-OECD # 203). Studies supporting the Acute Invertebrate and Acute Plant Endpoints were designated a reliability level of "1-Reliable without restriction", while the Acute Fish study was designated "2-Reliable with restrictions", as it was well documented but conducted prior to inception of GLPs.

Mammalian Toxicity Endpoints (Acute Toxicity, Repeated Dose Toxicity, Ames Mutagenicity and Chromosomal Aberration Testing, and Reproductive Toxicity) have all been filled by way of tests which either conformed directly with OECD test guidance or followed test designs similar to OECD guidance. The Acute Toxicity Endpoint was supported by a study which followed OECD guideline 401 and GLPs and was considered "1- Reliable without restriction". The Repeated Dose Toxicity Endpoint was met with an OECD guideline 408 study conducted in accordance with GLPs. It also was codified as "1- Reliable without restriction". Both the Ames test as well as an *in vitro* Chromosomal Aberration assay, used to support their respective Endpoints, were conducted by the US National Toxicology Program (NTP). The Ames test followed a study design equivalent to OECD guideline # 471 while the cytogenetics study was similar to, but not identical with, OECD guideline # 473. Thus, the Ames test was categorized as "1- Reliable without restriction" while the cytogenetics study was classified as "2- Reliable with restrictions".

A 2-Generation Reproduction Study fulfills the HPV requirements for the last Mammalian Toxicity Endpoint. This study was conducted to meet US EPA pesticide guidance for reproductive toxicity both in design and GLP compliance. While it deviated slightly from OECD guideline # 416, it has been classified as "1- Reliable without restriction" since it has been accepted by EPA to fulfill the Reproductive Toxicity data requirement for reregistration purposes.

Following is a tabular depiction of data availability and testing recommendations for p-Nitrophenol (PNP).

Table 1. Test Plan Matrix for para-Nitrophenol

	Info. Avail.?	OECD?	GLP?	Other Study?	Estimat. Method?	Accept-Able ?	Testing Recomm.?
PHYSICAL CHEMICAL							
Melting Point	Y	R	N	Y	-	Y	N
Boiling Point	Y	R	N	Y	-	Y	N
Vapor Pressure	Y	R	N	Y	-	Y	N
Partition Coefficient	Y	R	N	Y	-	Y	N
Water Solubility	Y	R	N	Y	-	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	N	L	Y	-	Y	N
Stability in Water	Y	N	N	N	-	Y	N
Biodegradation	Y	Y	L	Y	-	Y	N
Transport between Environmental Compartments (Fugacity)	Y	N	N	Y	Y	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	N	N	Y	-	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	L	Y	-	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	L	Y	-	Y	N
MAMMALIAN TOXICITY							
Acute Toxicity	Y	Y	Y	Y	-	Y	N
Repeated Dose Toxicity	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Mutation (Ames)	Y	Y	Y	Y	-	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	N	Y	Y	-	Y	N
Reproductive Toxicity	Y	N	Y	N	-	Y	N

Y = Yes; N = No; L = Likely, but not specified; R = Reputable Reference;
- = Not applicable

IV. DATA SET SUMMARY AND EVALUATION

The key studies used in this assessment to fulfill the HPV requirements have been placed in an Endpoint-specific matrix, and further discussed below. Robust Summaries for each study referenced can be found in Section VI of this dossier.

A. Chemical/Physical Properties

Table 2. Selected Chemical/Physical Properties of para-Nitrophenol (PNP)

Chemical	Boiling Pt. (^{o}C.)	Melting Pt.(^{o} C.)	Vapor Pressure (hPa @ 20 ^{o}C)	Water Solubility (mg/L)	Partition Coefficient (Log Kow)
p-Nitrophenol CAS No. 100-02-7	> 279	114	0.0067	16,000 @ 25 ^{o}C.	1.91

All HPV Endpoints for Chemical/Physical Properties have been completed with reliable information and taken from either primary or reputable textbook references (Table 2). The values, which are included in the Robust Summary section of this Dossier, have been internationally accepted as accurately depicting the properties of PNP and are cited in the IPCS Concise International Chemical Assessment Document (CICAD) for Mononitrophenols – Document No. 20 (2000) and/or cited as peer-reviewed references in the Hazardous Substances Data Bank (HSDB, 2002). They have been classified as "2-Reliable with restrictions". Additional Chemical/Physical property values can also be found in the IPCS CICAD No. 20 (2000) and the ECB IUCLID Dossier for P-Nitrophenol (2002).

In summary, these data indicate that PNP is a solid at room temperature and has a low vapor pressure. It has a low octanol:water partition coefficient and is soluble in water.

Conclusion – Adequate reference values are available to provide needed information on the Physical-Chemical Properties associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

B. Environmental Fate and Biodegradation

Extensive reviews and study citations in the Environmental studies area have been published on PNP, and are summarized in the IPCS CICAD (2000), in the HSDB (2002) and in the ECB IUCLID Dossier (2002) for PNP. Key studies have been selected for this

Dossier, which fairly depict the consensus conclusion/values for each of the HPV Endpoints listed (Table 3), and are summarized in the Robust Summary section of this Dossier. A comparative assessment of PNP Biodegradability employing 5 OECD Guideline 301 methods fulfills this HPV Endpoint; it has been designated as "1-Reliable without restriction". The molecular structure of PNP possesses only 2 functional groups (aromatic nitro and phenol), both of which are listed as types of Organic Functional Groups that are Generally Resistant to Hydrolysis (Table 7.1, Lyman et al, 1990). PNP is also considered "stable" in water by the German Umweltbundesamt, based on tests conducted in Germany (Schmidt-Bleek et al, 1982). PNP hydrolysis has also been reported as "nil" at pH 2, pH 7 and pH 12 (Capel and Larson, 1995). Photochemical degradation of PNP in an aquatic system has been evaluated in "the EPA Test" using the methodology of Leifer and Stern (Hustert et al, 1981). Estimation of Transport (Fugacity) was made using an EPA-accepted estimation model (EPIWIN, 2002). These values have been designated as "2-Reliable with restrictions". An overview of the known qualities of the environmental properties of PNP is provided below.

The Environmental Fate of PNP can be summarized, as follows. Upon release to the air, PNP would be expected to exist in a vapor state, based on its vapor pressure and would be degraded in the atmosphere by reaction with photo chemically-produced hydroxyl radicals; the half-life for this reaction in air is approximately 6 days (Table 3 - Photodegradation). However, PNP is extensively adsorbed to particles, in both the air and soil. Thus, as PNP is mostly particle-bound, its availability for photochemical reactions is limited (IPCS, 2000). Significant volatilization from soil or water to air is not expected, based on its Vapor Pressure (Table 2) and Henry's Law constant, respectively (IPCS, 2000). Atmospheric PNP, bound to particles, is expected to wash out to surface waters and soils by dry and wet deposition. Fugacity modeling (Table 3) indicates virtually complete allocation to water and soil; essentially no allocation was made to air or sediment (Table 3 - Fugacity). In aqueous solution, PNP appears stable (Table 3-Stability in Water). PNP has been classified as possessing low to moderate potential for soil sorption and can be decomposed under aerobic conditions, thus being classified as "Inherently Biodegradable" (IPCS, 2000)(Biodegradation – Table 3). Microbial decomposition can occur in different environmental compartments after adaptation of the microflora. Further biotic degradation under anaerobic conditions also occurs following extended acclimatization of microbial communities (Table 3 - Biodegradation). Measured values (IPCS, 2000; ECB IUCLID, 2002) indicate PNP has a low potential for bioaccumulation in aquatic species.

Table 3. Environmental Fate and Biodegradation Parameters for para-Nitrophenol (PNP)

Chemical	Biodegradation Rate	Stability in Water	Fugacity (%)	Photodegrad. Rate (T ½)
p-Nitrophenol CAS No. 100-02-7	~ 90 %	Stable	Air – 4.98 Water – 36.3 Soil – 58.7 Sediment – 0.02	5.7 (pH 5) 6.7 (pH 7) 13.7 (pH 9) .

Conclusion – Adequate studies following either OECD or EPA test guidance are available to provide needed information regarding the Biodegradation and Photodegradation of PNP. Information on Transport (Fugacity) were completed using EPIWIN, an accepted estimation-modeling program. As PNP possesses only functional groups generally known to be resistant to hydrolysis, testing for stability in water is not needed (SIDS Manual-new draft version). Therefore, no additional data development is warranted for these HPV Endpoints.

C. Aquatic Toxicity

The aquatic toxicity of PNP has been extensively reviewed (IPCS, 2000; HSDB, 2002; ECB IUCLID, 2002) and contains both acute and chronic toxicity studies on algae, invertebrates and fish. Studies selected for development of Robust Summaries are reported in Table 4 and depict the level of toxicity generally observed for these Endpoints within the overall dataset.

Both the Acute Invertebrate and the Acute Algae studies were conducted according to OECD test guidance # 202 and 201, respectively. While no mention was made of GLP compliance in the referenced publications, it is reasonable to assume both were conducted under GLP auspices as they followed OECD method guidance and were conducted to meet national regulatory mandates. Thus, both studies are considered "1-Reliable without restriction". The Acute Fish Toxicity study was conducted prior to inception of OECD/GLP guidance but is considered well documented and used methodology consistent with OECD guidance for this study type. This study is considered "2- Reliable with restrictions" only because it was conducted prior to codification of testing and GLP guidelines.

Table 4. Aquatic toxicity parameters for para-Nitrophenol (PNP)

Chemical	Fish LC 50 (mg/L)	Invertebrate LC50 (mg/L)	Algae EC50 (mg/L)
p-Nitrophenol CAS No. 100-02-7	5.8 (bluegill-96 hr)	22.0 (Daphnia-48 hr)	32.0 (96-hrs)

PNP is considered to be "Slightly Toxic" toward these and other aquatic species following acute testing (IPCS, 2000). Based on the pattern and release scenarios envisioned, PNP is expected to present a negligible risk to aquatic organisms.

Conclusion – Adequate studies which meet internationally accepted test guidelines are available on all 3 Aquatic Toxicity Endpoints to assess the acute aquatic toxic hazards associated with PNP. Therefore, no additional data development is needed for these HPV Endpoints.

D. Mammalian Toxicity Endpoints

A summary of available toxicity data used to fulfill the HPV Endpoints for Mammalian Toxicity is found in Table 5. Each report has been further summarized in the Robust Summary section of this Dossier.

Table 5. Mammalian Toxicity of p-Nitrophenol (PNP)

Chemical Name/ CAS no.	Acute Toxicity		Repeat Dose Toxicity			Reprotoxicity	Mutagenicity –In Vitro	
	OLD50 (rat)	DLD50 (rabbit)	90-day	28-day	Chronic	2-Gen.	Ames	Chrom. Aberr.
p-Nitro-phenol 100-02-7	230 mg/kg	> 5000 mg/kg	(oral-rat) NOEL 25 mg/kg/d	(inhal-rat) NOEL 5 mg/m3	(dermal-mouse) NOEL (systemic tox./carcin.) 160 mg/kg/d	(dermal-rat) NOEL (maternal-systemic) 250 mg/kg/d NOEL (reprotox) 250 mg/kg/d	Neg.- All strains +/- S9	Neg. (- S9) Pos. (+S9)

1.0 Acute Toxicity

Results of acute toxicity studies by both the oral and dermal routes of exposure have been conducted as summarized in Table 5. Both studies were conducted using study designs consistent with OECD Test Guidelines 401 and 402, respectively, under auspices of GLPs, and are deemed "1- Reliable without restriction". The acute rat oral toxicity study has been chosen as the key study to fulfill this HPV Endpoint. The acute rabbit dermal toxicity study is included as Supplemental information.

PNP is considered to be moderately toxic after acute oral exposure to rats. As there were no deaths or untoward signs of toxicity after acute dermal exposure well above generally accepted Limit Dose levels (1,000 mg/kg), PNP is considered practically non-toxic after acute dermal exposure to rabbits. However, based on the ability of PNP to produce methemoglobinemia in humans, this material is considered to be toxic in the workplace by all acute exposure routes. Additional acute toxicity values in animals can be found listed in the three compendium reports cited above.

Conclusion – A quality study, compliant with OECD/GLP guidance, is available to assess the Acute hazards associated with PNP. Therefore, no additional data development is needed for the Acute Toxicity HPV Endpoint.

2.0 Repeated Dose Toxicity

PNP has been adequately tested by several routes of exposure to define its Repeated Dose Toxicity. The key study used for this HPV assessment is cited in Table 5 and summarizes a 90-day subchronic rat study by the oral route. This study was conducted using a study design consistent with OECD Test Guideline 408, and under GLP auspices and is considered "1- Reliable without restriction". Early deaths related to PNP acute toxicity, and exacerbated by repeat dosing, occurred at dosage levels of 70 and 140 mg/kg/d. No other treatment-specific effects or organ pathology, including lack of involvement of male and female gonads (i.e. testes and ovaries), were affected. A NOEL of 25 mg/kg/d was established. A summary of this study and a 4-week Range Find study are found in the Robust Summary section of this Dossier. The IPCS CICAD (2000) also summarizes a 28-day oral gavage study (Andrae et al. 1981) with PNP at substantively higher levels, which resulted in excessive toxicity. This study was not considered in this review as it is not available in English and is superceded by the current study, which is of a longer exposure duration by the same route and has utilized a more appropriate selection of doses.

PNP also has been tested following inhalation exposure (Table 5). This study was not selected for inclusion as the key Repeated Dose Study, as it was conducted for a shorter (4-weeks) time period than the 90-day study referenced above. However, it too is considered "1- Reliable without restriction" and is included in the Robust Summary section of this Dossier.

It should be noted that no evidence of effects on the gonads was seen in either sex of rat in the studies cited above. Further, results of an 18-month chronic toxicity study in male and female mice (NTP, 1994) also cited in Table 5, resulted in no organ-related toxicity, including the gonads, up to the highest level tested (160 mg/kg/d, 3x/wk, 78 wks).

Conclusion - Thus, the Repeated Dose HPV Endpoint for PNP has been fulfilled with a 90-Day Subchronic study in rats deemed "1- Reliable without restriction". No further testing is needed for completion of information related to the Repeat Dose HPV Endpoint.

3.0 Mutagenicity and Chromosomal Aberrations

3.1 Mutagenicity Testing (Ames test)

PNP has been extensively tested in the standard Ames assay for point mutations (ECB IUCLID, 2002; IPCS CICAD, 2000). PNP elicited no mutagenic response in any of the *S. Typhimurium* tester strains employed, either with or without inclusion of metabolic activation. The Haworth et al, (1983) study, conducted on behalf of the NCI/NTP program, has been summarized in the Robust Summary section of this Dossier and its results are referenced in Table 5. Its design and documentation are such that it is considered equivalent to OECD guideline # 471 and thus is "1- Reliable without restriction" for this assessment. Additionally, PNP has been tested in the secondary tier *Drosophila* Sex-Linked Recessive Lethal assay; no mutagenicity was observed after either oral or injection dosing up to lethal doses by each route in this same NCI/NTP program (NTP, 1994). Oberly et al, 1990 reported that PNP elicited no mutagenic activity when tested in a CHO-HGPRT forward mutation assay in mammalian cells.

Thus, it is concluded that adequate testing of sufficient quality has been performed on PNP to evaluate the Ames Test (Point Mutation) HPV Endpoint; no further testing is needed for this Endpoint.

3.2 - Chromosomal Aberrations

As part of the NCI/NTP program (Galloway et al 1987), PNP was tested in the CHO cell *in vitro* assay to determine its capacity to induce chromosomal aberrations. A Robust Summary has been prepared for this study and its results are referenced in Table 5. PNP was negative for structural chromosome damage up to severely cytotoxic concentrations (>750 ug/ml) in a metabolic activation system-free environment. It did produce reproducible, dose-related and statistically significant increases in cells with structural chromosomal aberrations at levels of 1500 and 1700 ug/ml PNP after metabolic activation, although cells at these levels had undergone severe cell cycle delay. The quality of this study is considered to be "2- Reliable with restrictions", as it did not follow an established OECD protocol, yet was well documented and has been used for regulatory purposes. In a corresponding Sister Chromatid Exchange (SCE) assay

conducted in the same CHO cell test (Galloway et al. 1987), PNP produced no SCEs up to doses that caused severe cell cycle delay (25 ug/ml without S9 and 1700 ug/ml with S9).

The HPV Chromosomal Aberration Endpoint for testing of PNP has been fulfilled with adequately conducted and documented studies and no further testing is needed.

4.0 Reproductive Toxicity

A Two-Generation rat Reproduction Toxicity study of dermally applied PNP has been conducted (Table 5) and summarized in Dossier section VI - Robust Summaries. This study is considered adequate for assessment of this Endpoint as it has been accepted as such by IPCS (2000) and was judged "adequate" for US EPA pesticide reregistration (US EPA, 1998b). It was conducted under GLPs and followed OPPTS testing guidelines. Based on general acknowledgement of its scientific and regulatory acceptability, it has been judged as "1- Reliable without restriction" for purposes of this assessment. PNP was administered dermally in ethanol to groups of 12 male and 24 female rats at 50, 100 and 250 mg/kg/d. No indication of systemic toxicity was observed in either parental generation, although dermal irritation was observed at the site of application. No reproductive toxicity was observed at any dose tested in either the F1 or F2 matings. Both the adult systemic and reproductive toxicity NOELs are considered to be the highest dosage tested, i.e. 250 mg/kg/d.

In conclusion, the Reproductive Toxicity HPV Endpoint has been fulfilled with conduct of a Two-generation rat study which followed regulatory testing guidance, was conducted under GLPs, and accepted in support of pesticide reregistration. Thus, no further testing for this HPV Endpoint is required.

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VI. ROBUST STUDY SUMMARIES -

IUCLID Data Sets are appended